Rej ction under 35 U.S.C. § 112, second paragraph

The rejection of claims 1-5 as being indefinite has been noted. Reconsideration and withdrawal of this rejection is respectfully requested on the following grounds.

Claim 1 has been amended as discussed during the interview with the Examiner on June 18, 2002.

In light of the foregoing, reconsideration and withdrawal of this rejection is therefore respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

Rejection of claims 1 to 6 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention, has been noted. Reconsideration and withdrawal of this rejection is respectfully requested on the following grounds.

(A) As drawn to the human homologs of the gro-1 and hap-1 genes of *C. elegans*

Reconsideration of this rejection is respectfully requested on the following grounds.

The Examiner finds not persuasive the arguments presented previously pertaining to Bcl2 and the findings by Golovko et al. (2000) about human *gro-1*. In support of this, the Examiner specifies her belief that "the effect of an enzyme on a single cell or a simple organism such as *C. elegans* can be anticipated" but that "the effect of an enzyme on a complex multicellular organism cannot be construed solely from experiments on *C. elegans*". In support of her assertion, the Examiner cites a textbook by Alberts *et al.* (1989). The cited text refers to the problem of cell fate

determination, the genetic process by which, during development, cells are determined to be of various types (e.g. neuron, muscle, skin).

The Applicant maintains that the teachings from the *C. elegans gro-1* gene, supported by those of Golovko *et al.* (2000) and by an increasing body of knowledge that demonstrates the conservation of biochemical and organismal properties of genes and their encoded proteins among different phyla, enables one to anticipate the effect of an enzyme on a complex multicellular organism from experiments on *C. elegans*. 1) *C. elegans* is not fundamentally simpler than humans when the relation of gene product and physiology is considered. *C. elegans* has ~19,000 and humans ~35,000 genes. This is a less than a 2-fold difference. Therefore, the way gene function relates to the animal's physiology is not different in nature. 2) The process of fate determination mentioned in the citation by Alberts *et al.* is unrelated to any aspect of the disclosure or the claims of the present application. At no point is it claimed that *gro-1* is involved in developmental cell fate determination. 3) Since the publication of Alberts *et al.* (1989), the thinking about functional conservation, including at the organismal level, has changed significantly. It is now understood that developmental processes as well as metabolic and biochemical processes are conserved from invertebrates to vertebrates. In support of our statements we present a table with a few examples of recent studies demonstrating the functional equivalence of gene products in very different species, belonging to different phyla. We have chosen the examples to cover several modes of testing (vertebrate genes tested in invertebrate, including *C. elegans*, and in single cell models, and invertebrate genes tested in vertebrates), as well as covering genes involved in a variety of biological processes including metabolism, DNA function, development, cell fate determination and others. The few examples, out of many

more studies, provided in Table A below are a mere illustration of a now well recognized generality.

Table A

Examples of Evolutionary Conservation of Gene Function

Gene names	Gene origin	Tester organism	Biological pathway	Reference
Vertebrate genes tested in invertebrates				
KAL-1	Human	*C. elegans*	Neural morphogenesis	Rugarli et al., Development 129, 1283-1294 (2002)
Munc-18; *Unc-18*	Mouse	*C. elegans*	Cholinergic neurotransmission	Gengyo-Ando et al., The Journal of Neuroscience, November 1, 1996, *16*(21):6695– 6702
ARL2; *evl-20*	Human	*C. elegans*	Microtubule cytoskeleton	Antoshechkin and Han, Developmental Cell, Vol. 2, 579–591, May, 2002.
Presenilin, *sel-12*	Human	*C. elegans*	Intramembrane proteolysis	Baumeister et al., Genes Funct 1997 Apr;1(2):149-59
Pixt2/*unc-30*	Human	*C. elegans*	Transcriptional regulation: Neuronal differentiation	Westmoreland et al., The Journal of Neuroscience, September 1, 2001, 21(17):6810–6819
MyoD	Chicken Drosophila	*C. elegans*	Transcriptional regulation: Muscle differentiation	Zhang et al., Developmental Biology 208, 465–472 (1999)
Clk-1	Human	*C. elegans*	Ubiquinone biosynthesis	Takahashi et al., Biochemical and Biophysical Research Communications 286, 534–540 (2001)
Bcl2	Human	*C.elegans*	Programmed cell death	Vaux et al., Science 1992 Dec 18;258:1955-7
EZH2; ezh1; Enhancer of Zeste	Human, mouse	Drosophila, Yeast	Chromatin regulation; homeotic gene expression in development	Laible et al., The EMBO Journal Vol.16 No.11 pp.3219–3232, 1997
Smad4; *Medea*	Human	Drosophila	Signal transduction in embryonic patterning	Hudson et al., Development 125, 1407-1420 (1998)
Eed; ESC	Human	Drosophila	Homeotic gene expression in development	Wang et al., Genesis 26:67–76 (2000)

Vertebrate genes tested in yeast				
MTO1	Human	Yeast	Mitochondrial respiration	Li et al., Journal of Biological Chemistry Papers in Press. Published on May 14, 2002 as Manuscript M203267200
prp17	Human	Yeast	RNA splicing	Linsey et al., the journal of biological chemistry 273, No. 49, Issue of December 4, pp. 32771–32775, 1998
MMS19	Human, Drosophila	Yeast	Transcription	Queimado et al.,.Nuclei Acid Research, 29(9): 1884-1891, 2001.
Cdc5	Human, Drosophila	Yeast (*S. pombe*)	Transcriptional regulation; cell cycle progression	Ohi et al., MOLECULAR AND CELLULAR BIOLOGY, July 1998, p. 4097–4108 Vol. 18, No. 7
Ino1; hcp1; TGFR	Human	Yeast	Inositol metabolism	Nikawa et al., Gene, 171: 107-111, 1996.
CK2 (casein kinase II)	Human, *C. elegans*	Yeast	Cell cycle progression	Dotan et al., Biochemical and Biophysical Research Communications 288, 603–609 (2001)
sac6; fimbrin	Human	Yeast	Actin cytoskeleton	Adams et al., MOLECULAR AND CELLULAR BIOLOGY, Jan. 1995, p. 69–75
Invertebrate genes tested in vertebrates				
DAP3	*C. elegans*	Human	Programmed cell death	Kissil et al. The EMBO Journal Vol.18 No.2 pp.353–362, 1999,
Wnt; dishevelled	Drosophila	Xenopus	Developmental induction	Rothbacher et al., Dev Biol 1995 Aug;170(2):717-21
MyoD	Drosophila, *C. elegans*	Mouse	Transcriptional regulation: Muscle differentiation	Zhang et al., Developmental Biology 208, 465–472.(1999)
Tramtrack69	Drosophila	Human	Glial differentiation	Buzanska et al., J Neurosci Res 2001 Jul 1;65(1):17-23

While not all genes have been tested directly in heterologous systems, more general molecular studies have shown that analogous biological processes are supported by homologous molecular mechanisms, including at the organismal level.

For example, 1) the genes from the hox cluster have been found to be expressed colinearily with the antero-posterior axis and to direct its development in all animals, even animals with very different body plans (Ferrier DE and Holland PW, Nat Rev Genet 2001;2:33). 2) The molecular type of transcription factors that direct hematopoiesis in vertebrates also direct the production of blood cells in insects (Fosset N and Schulz RA, Diff 2001;69:83). 3) The development of eyes involves the function of the gene pax6 or a homologue in all animals, including vertebrates and invertebrates (Hanson I and Van Heyningen V, TIGS 1995;11:268). 4) Homologous genes are involved in the development of wings, whether of insects or of vertebrates, although these are not evolutionarily homologous structures (Laufer E *et al.*, Nature 1997;386:366). In view of the preceding comments, the Applicant maintains that the teachings from the *C. elegans gro-1* gene, supported by Golovko *et al.* (2000), enable to anticipate with certainty the properties of the human protein or the functioning of the GRO-1 polypeptide as a mediator of development and aging in humans, and that therefore claim 1 (as amended) contain only subject matter which is described in the specification and enables one skilled in the art to make and/or use the claimed invention. Thus, the Applicant respectfully submit that claim 1 of the present application are supported by the specification and that it is only a matter of adapting, without undue experimentation, what is described in the present application for the nematode, with homologous sequences identified in other organisms according to methodologies known in the art.

Reconsideration and withdrawal of this rejection is therefore respectfully requested.

(B) As drawn to functional fragments of human gro-1

Claim 1 as amended renders this objection moot.

(C) As drawn to hap-1, gop-1, gop-2 and gop-3

The cancelation of claims 2 to 6 renders this objection moot.

Reconsideration and withdrawal of these rejections is therefore respectfully requested.

Conclusion

It is submitted, therefore, that the claim is in condition for allowance. Reconsideration of the rejections is requested. Allowance of the claim at an early date is solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

David A. Jackson
Attorney for Applicant(s)
Registration No. 26,742

KLAUBER & JACKSON
411 Hackensack Avenue
Hackensack, New Jersey 07601
Tel: (201) 487-5800

Date: 6/27/2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The paragraph on Page 5, lines 17–19 of the Specification has been amended as follows:

(Amended) Fig. 5A-5B illustrate the alignment of *gro-1* (SEQ ID NO:2) with the published sequences of the *E. coli* (P16384) and yeast (P07884) enzymes;

The paragraph on Page 5, lines 29–30 as follows:

(Amended) Fig. 9A-9B illustrate a comparison of the conceptual amino acid sequences for GRO-1 (SEQ ID NO:2) and hgro-1p as deduced from SEQ ID NO:3;

Please amend the paragraph on Page 14, lines 1–28 as follows:

(Amended) Database searches also identified a homologous human expressed sequence tag (Genbank ID: Z40724). The human clone has been used to derive a sequence tagged site (STS). This means that the genetic and physical position of the human *gro-1* homologue is known. It maps to chromosome 1, 122.8 cR from the top of Chr 1 linkage group and between the markers D1S255 and D1S2861. This information was found in the UniGene database or the National Center for Biotechnology Information (NCBI). We have sequenced Z40724 by classical methods but found that Z40724 is not a full length cDNA clone as it does not contain an initiator methionine nor the poly A tail. We used the sequence of Z40724 to identify further clones by database searches. We found one clone (Genbank ID: AA332152) which extended the sequence 5′ by 28 nucleotides, as well as one clone (Genebank ID: AA121465) which extended the sequence substantially in the 3′ direction but didn't include the poly A tail. We then used AA121465 to identify an additional clone (AA847885) extending the sequence to the poly A tail. Fig. 8 shows the full sequence with the putative initiator ATG shown

in bold and the sequence of Z60724 is shown underlined. A comparison of the conceptual amino acid sequences for GRO-1 (SEQ ID NO:2) and hgro-1p as deduced from SEQ ID NO:3, is shown in Fig. 9. Amino acid identities are indicated by a dot. Both sequences contain a region with a zinc finger motif which is shown underlined.

Claims 1-6 have been amended as follows.

1. (Twice Amended) A *gro-1* ~~gene~~ polynucleotide encoding a hgro-1p protein, said *gro-1* polynucleotide being homologous to the *C. elegans gro-1* gene which encodes a protein set forth in SEQ ID NO:2, which functions in the regulation ~~has a function at the level~~ of cellular physiology, ~~involved in~~ developmental rate and longevity, ~~wherein gro-1 mutations cause a longer life and an altered cellular metabolism relative to the wild-type,~~ wherein ~~the~~ said *gro-1* ~~gene~~ polynucleotide comprises the nucleotide sequence set forth in SEQ ID NO:3 or any functional fragment thereof having said function in the regulation of cellular physiology, developmental rate and longevity.

2. (Canceled)

3. (Canceled)

4. (Canceled)

5. (Canceled)

6. (Canceled)